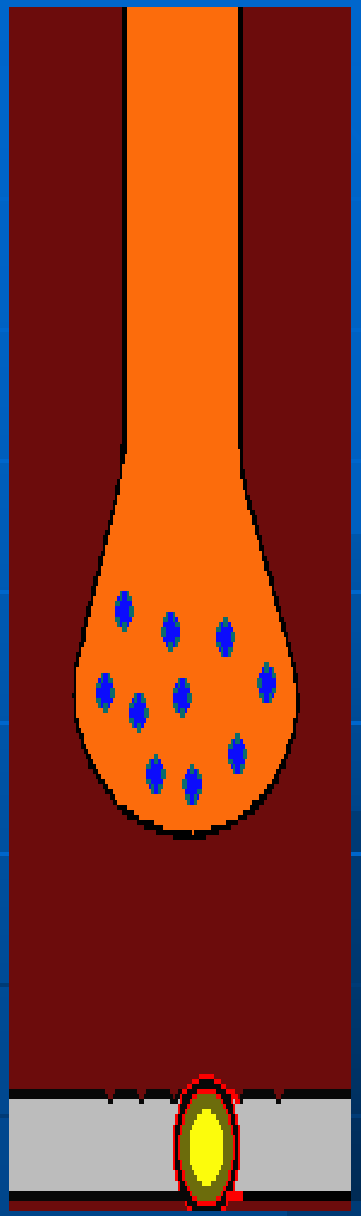
GABA receptors



Prof.Dr.Nuray Arı, 2018

Key Points

GABA (γ-aminobutyric acid) is the predominant inhibitory neurotransmitter in the central nervous system (CNS).

There are two types of GABA receptor in the CNS: $GABA_A$ receptors (GABAARs) and $GABA_B$receptors.

The central role of the GABAAR to sedation and anesthesia is evident from the number of sedative and anesthetic agents that exert their hypnotic and amnesic effects by stimulating the GABAAR: nitrous oxide, isoflurane, sevoflurane, desflurane, propofol, etomidate, methohexital, thiopental, and benzodiazepines.

Newer GABAAR agonists have been developed based on parent compounds, which may provide alternatives to the traditional GABAAR agonists, but with a more favorable pharmacokinetic and pharmacodynamic profile.

CNS Drugs. 2017 Oct;31(10):845-856. doi: 10.1007/s40263-017-0463-7. ***The Role of GABA Receptor Agonists in Anesthesia and Sedation.*** *Brohan J[1], Goudra BG.*

•Highlights

- Many clinical CNS depressants act by enhancing $GABA_A$receptor-mediated inhibition .
- Some anxiolytic and sedative drugs act on $GABA_A$R subtype-dependent ECD sites .
- General anesthetics, alcohols, steroids act at $GABA_A$R subunit-interface TMD sites
- Ethanol at high anesthetic doses acts on $GABA_A$R subtype-dependent TMD sites .
- Ethanol at low intoxicating doses acts at $GABA_A$R subtype-dependent ECD sites .

•*Neuropharmacology. 2018 Jan 31. pii: S0028-3908(18)30036-4. doi: 10.1016/j.neuropharm.2018.01.036. [Epub ahead of print]* ***GABAA receptor: Positive and negative allosteric modulators.*** *Olsen RW.*

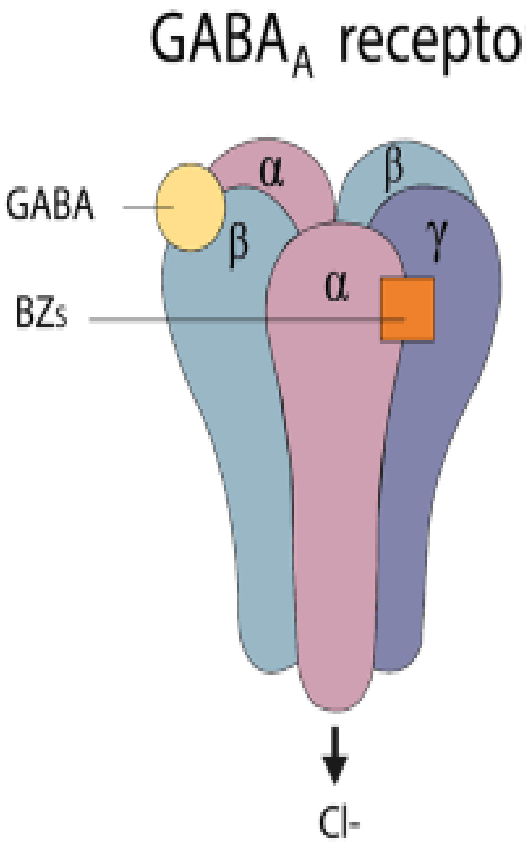
Adv Pharmacol. 2015;73:167-202. doi: 10.1016/bs.apha.2014.11.005..

Allosteric ligands and their binding sites define γ-aminobutyric acid (GABA) type A receptor subtypes.

Olsen RW.

GABAA receptors (GABA(A)Rs) mediate rapid inhibitory transmission in the brain. GABA(A)Rs are ligand-gated chloride ion channel proteins and exist in about a dozen or more heteropentameric subtypes exhibiting variable age and brain regional localization and thus participation in differing brain functions and diseases. GABA(A)Rs are also subject to modulation by several chemotypes of allosteric ligands that help define structure and function, including subtype definition. The channel blocker picrotoxin identified a noncompetitive channel blocker site in GABA(A)Rs. This ligand site is located in the transmembrane channel pore, whereas the GABA agonist site is in the extracellular domain at subunit interfaces, a site useful for low energy coupled conformational changes of the functional channel domain. Two classes of pharmacologically important allosteric modulatory ligand binding sites reside in the extracellular domain at modified agonist sites at other subunit interfaces: the benzodiazepine site and the high-affinity, relevant to intoxication, ethanol site. The benzodiazepine site is specific for certain GABA(A)R subtypes, mainly synaptic, while the ethanol site is found at a modified benzodiazepine site on different, extrasynaptic, subtypes. In the transmembrane domain are allosteric modulatory ligand sites for diverse chemotypes of general anesthetics: the volatile and intravenous agents, barbiturates, etomidate, propofol, long-chain alcohols, and neurosteroids. The last are endogenous positive allosteric modulators. X-ray crystal structures of prokaryotic and invertebrate pentameric ligand-gated ion channels, and the mammalian GABA(A)R protein, allow homology modeling of GABA(A)R subtypes with the various ligand sites located to suggest the structure and function of these proteins and their pharmacological modulation.

GABA and $GABA_A$ receptor



- GABA is a major inhibitory neurotransmitter
- Neuronal inhibition by increasing chloride ion conductance
- Inhibits brain regions involved in wakefulness

Watson, C. J., Baghdoyan, H. A., & Lydic, R. (2012). Neuropharmacology of sleep and wakefulness: 2012 update. *Sleep medicine clinics*, 7(3), 469-486.

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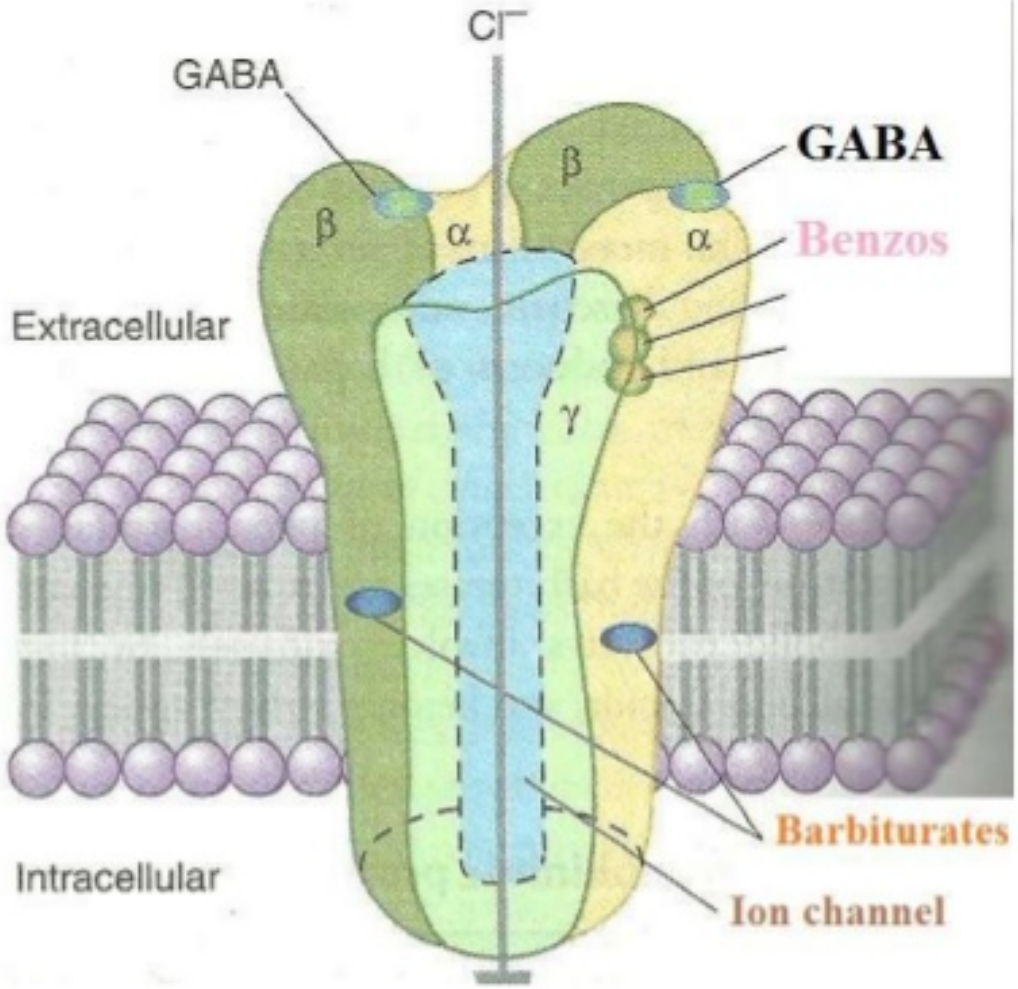
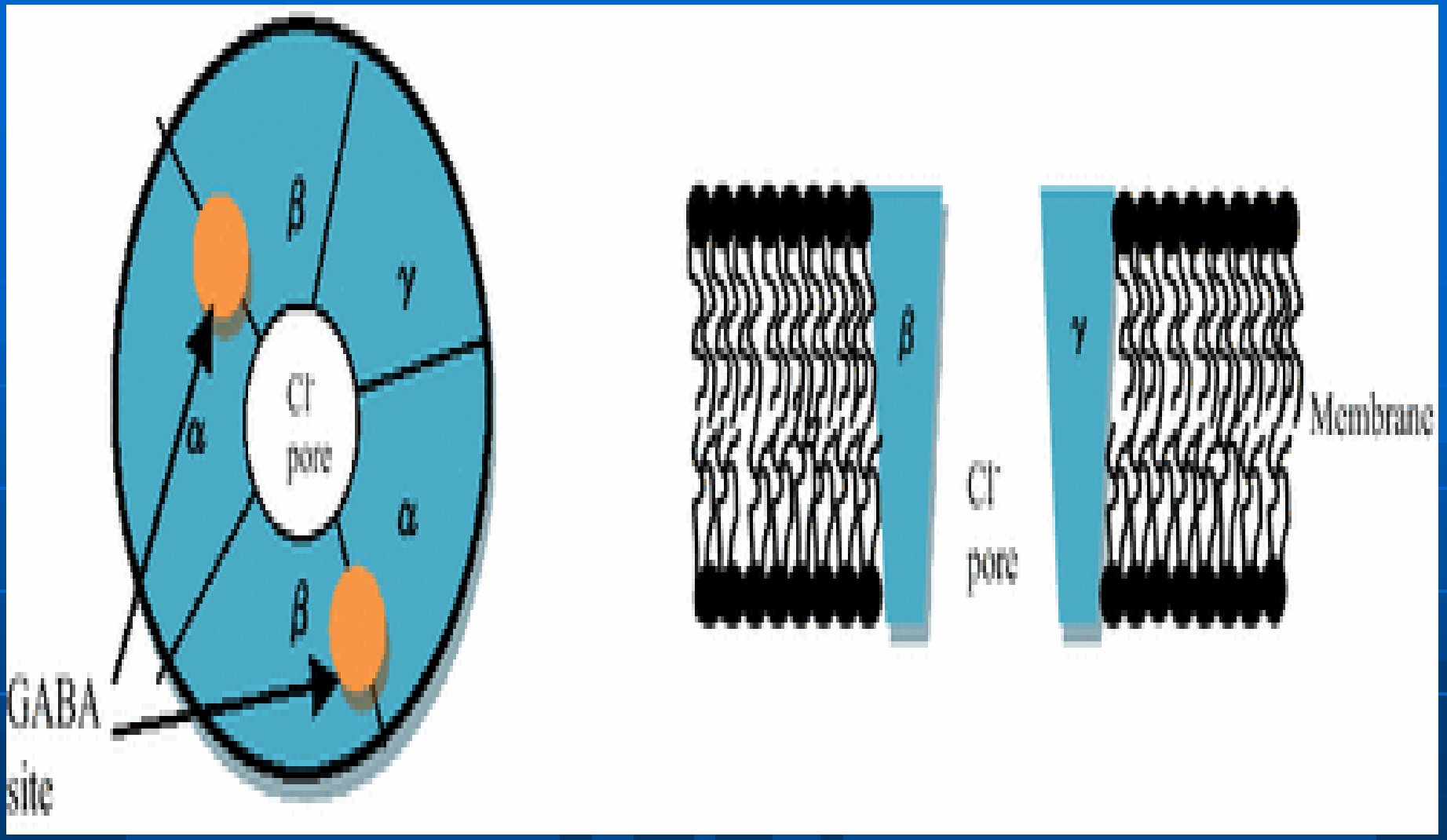
Benzodiazepine Binding Site on $GABA_A$



$GABA_A$ =
α1 α2 α3 α4 α5 α6
β1 β2 β3 β4
γ1 γ2 γ3
δ
ε
π
ρ

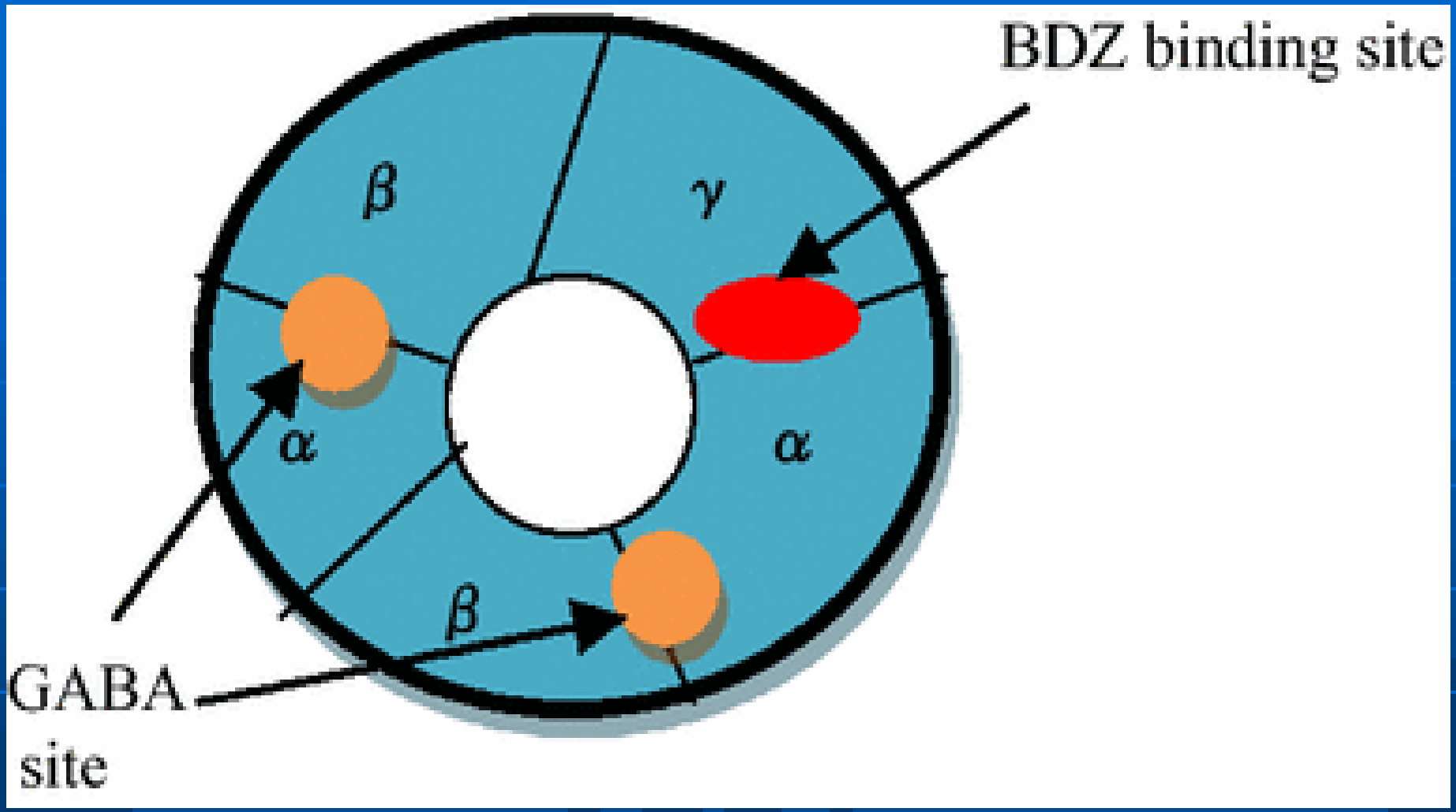
Location: Binding
α1β2 : GABA
α1γ2 : benzodiazepines

Trevor & Way (2012). Sedative-Hypnotic Drugs. In Katzung's Basic & Clinical Pharmacology, p. 374.



Basic structure of the pentameric transmembrane $GABA_A$ receptor.

CNS Drugs. 2017 ;31(10):845-856. doi: 10.1007/s40263-017-0463-7. ***The Role of GABA Receptor Agonists in Anesthesia and Sedation.*** *Brohan J, Goudra BG.*



Location of benzodiazepine binding site on the GABAAR.

CNS Drugs. 2017 Oct;31(10):845-856. doi: 10.1007/s40263-017-0463-7. ***The Role of GABA Receptor Agonists in Anesthesia and Sedation.*** *Brohan J, Goudra BG.*